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# NOTICE OF ALLOWANCE AND FEE(S) DUE

25885

7590

08/10/2009

ELI LILLY & COMPANY PATENT DIVISION P.O. BOX 6288 INDIANAPOLIS, IN 46206-6288 EXAMINER

BLANCHARD, DAVID J

ART UNIT PAPER NUMBER

1643

DATE MAILED: 08/10/2009

	APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.	
_	10/555,407	06/08/2007	Dale L. Ludwig	X-18524	7544	

TITLE OF INVENTION: FULLY HUMAN ANTIBODIES DIRECTED AGAINST THE HUMAN INSULIN-LIKE GROWTH FACTOR-1 RECEPTOR

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	\$1510	\$300	\$0	\$1810	11/10/2009

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

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APPLICATION NO.	FILING DATE		FIRST NAMED INVENTOR			ATTORNEY DOCKET NO.		CONFIRMATION NO.	L
10/555,407 ITLE OF INVENTION	06/08/2007 FULLY HUMAN AN	TIBODIES DIRECTED A	Dale L. Ludwig AGAINST THE HUM.	AN II	NSULIN-LIKE GR	OWT	X-18524 H FACTOR-1 RECE	7544 PTOR	
APPLN, TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE D	UE	PREV. PAID ISSUE	FEE	TOTAL FEE(S) DUE	DATE DUE	brack
nonprovisional	NO	\$1510	\$300		\$0		\$1810	11/10/2009	
EXAM	INER	ART UNIT	CLASS-SUBCLASS						
BLANCHAR	D, DAVID J	1643	530-388150						_
Change of correspondence address or indication of "Fee Address" (37 FR 1.363).  Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.  "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. Use of a Customer Number is required.							_		
PLEASE NOTE: Uni recordation as set fort (A) NAME OF ASSIG	less an assignee is identi h in 37 CFR 3.11. Comp GNEE	A TO BE PRINTED ON T ified below, no assignee oletion of this form is NO categories (will not be pr	data will appear on t T a substitute for filing (B) RESIDENCE: (C	he pa g an a CITY	tent. If an assigned ssignment. and STATE OR CO	OUNT	RY)	_	
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_ 0	<b>tus</b> (from status indicated s SMALL ENTITY statu	,	☐ b. Applicant is no	long	er claiming SMALI	L EN'I	TTY status. See 37 CF	FR 1.27(g)(2).	_
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10/555,407 06/08/2007		Dale L. Ludwig	X-18524 7544		
25885 75	90 08/10/2009		EXAM	INER	
ELI LILLY & CO	OMPANY	BLANCHARD, DAVID J			
PATENT DIVISIO	)N		ART UNIT	PAPER NUMBER	
P.O. BOX 6288 INDIANAPOLIS,	IN 46206-6288		1643 DATE MAILED: 08/10/200	9	

# **Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)**

(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 263 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 263 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 (571)-272-4200.

	Application No.	Applicant(s)		
	10/555,407	LUDWIG, DALE L.		
Notice of Allowability	Examiner	Art Unit		
	David J. Blanchard	1643		
The MAILING DATE of this communication appeal All claims being allowable, PROSECUTION ON THE MERITS IS herewith (or previously mailed), a Notice of Allowance (PTOL-85) NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIOF of the Office or upon petition by the applicant. See 37 CFR 1.313	(OR REMAINS) CLOSED in this apport or other appropriate communication IGHTS. This application is subject to	olication. If not included will be mailed in due course. <b>THIS</b>		
2. The allowed claim(s) is/are <u>12-14,23-34, 41-49 and 57-60</u>	(renumbered as claims 1-28).			
<ol> <li>Acknowledgment is made of a claim for foreign priority ur</li> <li>a) All b) Some* c) None of the:</li> <li>1. Certified copies of the priority documents have</li> <li>2. Certified copies of the priority documents have</li> <li>3. Copies of the certified copies of the priority documents have</li> <li>International Bureau (PCT Rule 17.2(a)).</li> </ol>	be been received. been received in Application No			
* Certified copies not received:				
Applicant has THREE MONTHS FROM THE "MAILING DATE" noted below. Failure to timely comply will result in ABANDONN THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.		complying with the requirements		
4. A SUBSTITUTE OATH OR DECLARATION must be subm INFORMAL PATENT APPLICATION (PTO-152) which give				
5. CORRECTED DRAWINGS (as "replacement sheets") mus	st be submitted.			
(a) 🔲 including changes required by the Notice of Draftspers	son's Patent Drawing Review ( P <b>T</b> O-	948) attached		
1) 🔲 hereto or 2) 🔲 to Paper No./Mail Date	•			
(b) ☐ including changes required by the attached Examiner's Paper No./Mail Date	s Amendment / Comment or in the C	Office action of		
Identifying indicia such as the application number (see 37 CFR 1 each sheet. Replacement sheet(s) should be labeled as such in t				
DEPOSIT OF and/or INFORMATION about the depo attached Examiner's comment regarding REQUIREMENT				
Attachment(s)  1. ☐ Notice of References Cited (PTO-892)  2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)	5. ☐ Notice of Informal P 6. ☐ Interview Summary	(PTO-413),		
3. ☑ Information Disclosure Statements (PTO/SB/08),	re nent/Comment			
Paper No./Mail Date <u>See Continuation Sheet</u> 4. Examiner's Comment Regarding Requirement for Deposit of Biological Material		ent of Reasons for Allowance		
/David J Blanchard/ Primary Examiner, Art Unit 1643				

Continuation of Attachment(s) 3. Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date: 12/23/08 (3 pages); 12/23/08 (8 pages).

Art Unit: 1643

#### DETAILED ACTION

1. Claims 1-11, 15-22, 35-40 and 50-56 are cancelled. Claims 12-14, 23-27 and 30 have been amended. Claims 57-60 have been added.

2. Claims 12-14, 23-34, 41-49 and 57-60 are pending.

#### Election/Restrictions

- 3. Applicant's election of the Invention of Group I, claims 12-14, 23-33 and newly added claims 57-60 in the reply filed on 28 may 2009 is acknowledged.
- 4. Claim 34 and 41-49 directed to an allowable product. Pursuant to the procedures set forth in MPEP § 821.04(b), claims 34 and 41-49, directed to the process of making or using the allowable product, previously withdrawn from consideration as a result of a restriction requirement, are hereby rejoined and fully examined for patentability under 37 CFR 1.104. Cancelled claims 19-22 (Group II), 34 and 36-40 (Groups III, IV and V), directed to the invention(s) of nucleic acids, vectors and host cells encoding a human antibody or fragment thereof that binds IGF-IR (Group I) and methods of treating acromegaly, retinal neovascularization and psoriasis comprising administering a human antibody or fragment thereof that binds IGF-IR (Groups III, IV and V, respectively) have NOT been rejoined.

Because a claimed invention previously withdrawn from consideration under 37 CFR 1.142 has been rejoined, the restriction requirement among groups I and VI as set forth in the Office action mailed on 28 April 2009 is hereby WITHDRAWN. For clarity, it is noted that the restriction requirement among groups II, III, IV and V as set forth in the Office action mailed on 28 April 2009 is MAINTAINED. In view of the withdrawal of the restriction requirement as to the rejoined inventions, applicant(s) are advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Once the restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Art Unit: 1643

### Information Disclosure Statement

5. The Information Disclosure Statement (IDS) filed 23 December 2008 (3 pages) and 23 December 2008 (twelve pages) have been considered by the Examiner. A signed and initialed copy of each IDS is included with the instant Office Action.

#### **Examiner's Amendment**

6. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Sanjay M. Jivraj on 29 July 2009

#### The claims are amended as follows:

- 12. (Currently Amended) An isolated human antibody or fragment thereof, which specifically binds to insulin-like growth factor-I receptor (IGF-IR) comprising complementarity-determining region (CDR) regions (CDRs) having the amino acid sequence SEQ ID NO:14 at V<sub>H</sub>CDR1, SEQ ID NO:16 at V<sub>H</sub>CDR2, SEQ ID NO:18 at V<sub>H</sub>CDR3, SEQ ID NO:20 or 26 at V<sub>L</sub>CDR1, SEQ ID NO:22 or 28 at V<sub>L</sub>CDR2, and SEQ ID NO:24 or 30 at V<sub>L</sub>CDR3.
- 13. (Currently Amended) The antibody or antigen binding fragment thereof of Claim 12, which comprises SEQ ID NO:14 at V<sub>H</sub>CDR1, SEQ ID NO:16 at V<sub>H</sub>CDR2, SEQ ID NO:18 at V<sub>H</sub>CDR3, SEQ ID NO:20 at V<sub>L</sub>CDR1, SEQ ID NO:22 at V<sub>L</sub>CDR2, and SEQ ID NO:24 at V<sub>L</sub>CDR3.
- 14. (Currently Amended) The antibody or antigen binding fragment thereof of Claim 12, which comprises SEQ ID NO:14 at V<sub>H</sub>CDR1, SEQ ID NO:16 at V<sub>H</sub>CDR2, SEQ ID NO:18 at V<sub>H</sub>CDR3, SEQ ID NO:26 at V<sub>L</sub>CDR1, SEQ ID NO:28 at V<sub>L</sub>CDR2, and SEQ ID NO:30 at V<sub>L</sub>CDR3.

Art Unit: 1643

Claims 15-22 (Cancelled)

23. (Currently Amended) A pharmaceutical composition comprising the antibody or antibody

fragment thereof of Claim 12 and a pharmaceutically acceptable carrier.

24. (Currently Amended) A conjugate comprising the antibody or antibody fragment thereof of

Claim 12 linked to a cytotoxic agent.

25. (Currently Amended) A conjugate comprising the antibody or antibody fragment thereof of

Claim 12 linked to a label.

26. (Currently Amended) A therapeutic composition effective to inhibit growth of human tumor

cells that express IGF-IR, which composition comprises the antibody or antigen binding

fragment thereof of Claim 12.

27. (Currently Amended) The therapeutic composition of Claim 26, which further comprises an

antineoplastic agent.

28. (Original) The therapeutic composition of Claim 27, wherein the anti-neoplastic agent is an

inhibitor of topoisomerase I or topoisomerase II.

29. (Original) The therapeutic composition of Claim 27, wherein the anti-neoplastic agent is

selected from the group consisting of irinotecan, camptothecan, and etoposide.

30. (Currently Amended) A therapeutic composition effective to promote regression of human

tumors that express IGF-IR, which composition comprises the antibody or antibody fragment

thereof of Claim 12.

Art Unit: 1643

- 31. (Original) The therapeutic composition of Claim 30, which further comprises an antineoplastic agent.
- 32. (Original) The therapeutic composition of Claim 31, wherein the anti-neoplastic agent is an inhibitor of topoisomerase I or topoisomerase II.
- 33. (Currently Amended) The therapeutic composition of Claim 31, wherein the anti-neoplastic agent is selected from the group consisting of irinotecan, camptothecan, [[or]] and etoposide.
- 34. (Currently Amended) A method of neutralizing the activation of [[IGF-LR]] <u>IGF-IR</u>, which comprises administering to a mammal an effective amount of the antibody or antibody fragment <u>thereof</u> of Claim 12

Claims 35-40 (Cancelled)

- 41. (Currently Amended) A method of reducing tumor growth which comprises administering to a mammal an effective amount of the antibody or antibody fragment thereof of Claim 12.
- 42. (Original) The method of Claim 41, which further comprises administering an effective amount of an anti-neoplastic agent.
- 43. (Original) The method of Claim 42, wherein the anti-neoplastic agent is an inhibitor of topoisomerase I or topoisomerase II.
- 44. (Original) The method of Claim 42, wherein the anti-neoplastic agent is selected from the group consisting of irinotecan, camptothecan, and etoposide.
- 45. (Currently Amended) A method of promoting tumor regression which comprises administering to a mammal an effective amount of the antibody or antibody fragment thereof of

Art Unit: 1643

Claim 12.

46. (Original) The method of Claim 45, which further comprises administering an effective

amount of an anti-neoplastic agent.

47. (Original) The method of Claim 46, wherein the anti-neoplastic agent is an inhibitor of

topoisomerase II or topoisomerase II.

48. (Original) The method of Claim 46, wherein the anti-neoplastic agent is selected from the

group consisting of irinotecan, camptothecan, and etoposide.

49. (Original) The method of any one of Claims 41 to 48, wherein the tumor is a breast tumor,

colorectal tumor, pancreatic tumor, ovarian tumor, lung tumor, prostate tumor, bone or soft tissue

sarcoma or myeloma.

Claims 50-56 (Cancelled)

57. (Currently Amended) An antibody isolated human antibody or fragment thereof comprising

[[a]] the heavy chain variable domain represented by of SEQ ID NO:2 and [[a]] the light

chain variable domain represented by of SEQ ID NO:6.

58. (Currently Amended) An antibody isolated human antibody or fragment thereof comprising

[[a]] the heavy chain variable domain represented by of SEQ ID NO:2 and [[a]] the light

chain variable domain represented by of SEQ ID NO:10.

59. (Currently Amended) The antibody of Claims 57-58 Claims 57 or 58, wherein said antibody

has an IgG1 isotype.

60. (Currently Amended) A pharmaceutical composition comprising the antibody of Claims 57-

59 Claims 57 or 58 and a pharmaceutically acceptable carrier.

Art Unit: 1643

### Amendments to the specification

On page 1, please delete paragraph [0001] and replace it with the following paragraph:

[0001] This application claims the benefit of United States Provisional Application 60/467,177, filed May 1, 2003 priority of and is a U.S. national phase application of PCT/US2004/013852, filed May 3, 2004, which claims priority of U.S. Provisional Application No. 60/467,177, filed May 1, 2003.

Please Amend Paragraphs 15-26 on pages 6 and 7 as follows;

[0015] Figure 1 depicts the nucleotide sequence of the 2F8 heavy chain variable domain (SEQ ID NO:1).

[0016] Figure 2 depicts the amino acid sequence of the 2F8 heavy chain variable domain. CDRs are in bold and underlined (SEQ ID NO:2).

[0017] Figure 3 depicts the nucleotide sequence of the complete 2F8 heavy chain (underline: secretory signal sequence; italics: IgGl constant region) (SEQ ID NO:3).

[0018] Figure 4 depicts the amino acid sequence of the complete 2F8 heavy chain (underline: secretory signal sequence; bold: CDRs; italics: IgGI constant region) (SEQ ID NO:4).

[0019] Figure 5 depicts the nucleotide sequence of the 2F8 light chain variable domain (<u>SEQ ID</u> NO:5).

[0020] Figure 6 depicts the amino acid sequence of the 2F8 light chain variable domain. CDRs are in bold and underlined (SEQ ID NO:6).

[0021] Figure 7 depicts the nucleotide sequence of the complete 2F8 light chain (underline: secretory signal sequence; italics: IgGI constant region) (SEQ ID NO:7).

[0022] Figure 8 depicts the amino acid sequence of the complete 2F8 light chain (underline: secretory signal sequence; bold: CDRs; italics: IgGI constant region) (SEQ ID NO:8).

[0023] Figure 9 depicts the nucleotide sequence of the A12 light chain variable domain (<u>SEQ ID NO:9</u>).

Art Unit: 1643

[0024] Figure 10 depicts the amino acid sequence of the Al2 light chain variable domain. CDRs are in bold and underlined (SEQ ID NO:10).

[0025] Fig. 11 depicts the nucleotide sequence of the complete A12 light chain (underline: secretory signal sequence; italics: IgGl constant region) (SEQ ID NO:11).

[0026] Figure 12 depicts the amino acid sequence of the complete A12 light chain (underline: secretory signal sequence; bold: CDRs; italics: IgGl constant region) (SEQ ID NO:12).

Please Amend Paragraph 81 on page 18 as follows;

[0081] In another embodiment, the present antibodies, or fragments thereof, can have a heavy chain variable region of SEQ ID NO: 1 SEQ ID NO: 2 and/or a light chain variable region selected from SEQ ID NO:5 or SEQ ID NO:6 SEQ ID NO:6 or SEQ ID NO:10. IMC-A12 is a particularly preferred antibody of the present invention. This antibody has human V<sub>H</sub> and V<sub>L</sub> framework regions (FWs) as well as CDRs. The V<sub>H</sub> variable domain of IMC-A12 (SEQ ID NO:1 SEQ ID NO:2) has three CDRs corresponding to SEQ ID NOs:14, 16, and 18 and the V<sub>L</sub> domain (SEQ ID NO:5 SEQ ID NO:10) has three CDRs corresponding to SEQ ID NOS:20, 22, and 24 SEQ ID NOS:26, 28, and 30. IMC-2F8 is another preferred antibody of the present invention. This antibody also has human V<sub>H</sub> and V<sub>L</sub> framework regions (FWs) and CDRs. The V<sub>H</sub> variable domain of IMC-2F8 is identical to the V<sub>H</sub> variable domain of IMCA12. The V<sub>L</sub> domain of IMC-2F8 (SEQ ID NO:9 SEQ ID NO:6) has three CDRs corresponding to SEQ ID NOS:26, 28, and 30 SEQ ID NOS:20, 22, and 24.

### **Examiner's Statement of Reasons for Allowance**

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Art Unit: 1643

Claims 12-14, 23-33 and 57-60 are free of the prior art. The prior art does not teach or fairly suggest an isolated human antibody or fragment thereof comprising the recited heavy and light chain CDR sequences or an antibody comprising the heavy chain variable domain of SEQ ID NO:2 and the light chain variable domain of SEQ ID NO:6 or 10.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <a href="http://pair-direct.uspto.gov">http://pair-direct.uspto.gov</a>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Blanchard/ Primary Examiner, A.U. 1643